It is respectfully submitted that WO 91/04748 does not disclose an ophthalmological formulation comprising an inhibitor of TGFβ in an ophthalmologically acceptable carrier.

Indeed, the cited document does not describe pharmaceutical formulations containing an inhibitor of TGFβ. The document refers to treating or arresting various pathologies by providing an agent to suppress the activity of TGFβ or refers to contacting a tissue with an agent to suppress the activity of TGFβ. The document does not describe the form in which the agent is provided or brought into contact with the tissue. The only example in the cited document which describes the administration of an inhibitor of TGFβ to an animal is Example VII. That example describes the injection of "anti-TGF-β (78-109)". However, the WO publication does not describe the form in which the anti-TGFβ was administered. Similarly, the other examples do not describe pharmaceutical formulations containing inhibitors of TGFβ.

Accordingly, it is respectfully submitted that WO 91/04748 does not teach compositions containing an inhibitor of TGFβ. Further, the document does not teach ophthalmological formulations comprising an inhibitor of TGFβ as claimed in claims 19 to 23.

Claims 14 to 18 and 34 to 38

The Examiner has stated that WO 91/04748 teaches the use of inhibitors of TGFβ for the treatment of different fibrotic disorders. The Examiner considers the use of claims 14 to 18 and 34 to 38 to be inherently taught by that document.

Claims 14 to 18 define a method of preventing or controlling cataract or after-cataract formation in the eye of a mammalian subject which comprises the step of administering to the subject an effective amount of one or more inhibitors of TGFβ. Claims 34 to 38 define a method of use of inhibitors of TGFβ in the manufacture of an ophthalmological formulation for preventing or controlling cataract or after-cataract formation.

Significantly, it is respectfully submitted that WO 91/04748 does not teach or suggest the use of inhibitors of TGFβ in the prevention or control of cataract or after-cataract formation in the eye of a mammal. There is no mention in the cited document of the prevention or control of cataract or after-cataract formation.

The concentration of injected immunoglobulin that would reach the ocular media surrounding the lens in the eye of the rats would be much less than 700 μg/ml for the following reasons. The lens is housed in specialized chambers in the eye that are filled with fluid (the ocular media known as aqueous and vitreous humour), and therefore to reach the lens cells the injected immunoglobulin would have to pass from the blood stream into these fluids. Serum proteins including antibodies do enter these fluids, but entry is restricted and these fluids contain much lower concentrations of serum proteins than are present in the circulating blood. For example, in the monkey eye, the total protein concentration of the aqueous humour in the anterior chamber of the eye is only 0.05-0.2% of the plasma protein concentration (Barsotti M.F. – et al. Invest. Ophthalmol. Vis. Sci. 1992; 33: 581-585; See concurrently filed IDS). In other species, it has been shown that the total protein content of the vitreous humour is only about 1-2% of the total

serum protein (Chen C.H. and Chen S.C. Exp. Eye Res. 1981; 32: 381-388; See concurrently filed IDS).

Based on this information, the concentration of the injected immunoglobulin reaching the fluid bathing the lens of the eye of the rat would be about 0.4-14 μg/ml assuming that all serum proteins transferred uniformly into these chambers. However, this is probably an overestimate because the permeability barrier through which the serum proteins must pass to reach the lens restricts the passage of immunoglobulins more than smaller proteins (Dernouchamps J.P. and Heremans J.F. Exp. Eye Res. 1975; 21: 289-297; See concurrently filed IDS). The concentration of 0.4-14 μg/ml (or less) is much lower than the about 700 μg/ml concentration of injected immunoglobulin in the blood. There is nothing in the cited document to suggest that such a low concentration would be effective in the prevention or control of cataract or after-cataract formation in the eye of the rats treated.

In example 2 of the specification for the present application, the inventors used a commercial pan-specific antibody, which blocks the effects of all know mammalian isoforms of TGFβ, to inhibit the cataractogenic changes in lens cells at a concentration of 50 μg/ml. This antibody seems to have been inherently more effective than the anti-TGFβ antiserum used in WO 91/04748; it gave virtually complete blocking of TGFβ2-induced cataractous changes in lens cells at 50 μg/ml (see example 2). In contrast, a 1:10 dilution of the antiserum used in WO 91/04748 (corresponding to a concentration about 800 μg/ml of immunoglobulin) was needed to block TGF-β1's effects in culture (See Border et al., 1990, Figure 1; See concurrently filed IDS).

Unlike the claims which were the subject of the Novitski case cited by the Examiner, claims 14 to 18 of the present application refer to the amount of the agent administered (the claims refer to the administration of "an effective amount of the inhibitor of TGFβ"). As noted in the Novitski case, the claims the subject of that decision were not limited to the degree of protection from plant pathogenic nematodes.

Further, claims 14 to 18 define a method of preventing or controlling cataract or after-cataract formation in the eye of a mammalian subject comprising administering an effective amount of one or more inhibitors of TGFβ.

WO 91/04748 does not teach the administration of an inhibitor of TGFβ in an amount effective to prevent or control cataract or after-cataract formation in the eye of a mammalian subject.

WO 91/04748 teaches the treatment of pathologies characterized by an accumulation of extracellularmatrix components by providing an agent to suppress the activity of TGFβ. The cited document does not describe the amounts of the agent to suppress the activity of TGFβ provided to treat such conditions. The only description in the cited document of the administration of an inhbitor of TGFβ to a whole animal is in Example VII. The cited document states that in that example the rats were treated with "injections of anti-TGF-β (78-109)". The document does not describe the form in which the anti-TGF-β was administered nor the amount of the anti-TGF-β injected. Accordingly, the document does not describe a method involving the administration to an animal of an amount of an inhibitor of TGFβ effective to prevent or control cataract or after-cataract formation in the eye of the animal.

Further, in the document cited by the Examiner, the agent for suppressing the activity of TGFβ is administered for treating conditions other than cataract or after-cataract formation. The agent would be administered by a route and in amounts suitable for the treatment of the conditions sought to be treated, not in amounts intended for the prevention or control of cataract or after-cataract formation.

As mentioned above, the only description in the cited document of the administration of an inhibitor of TGFβ to an animal is in Example VII. Although the amount of the inhibitor of TGFβ administered is not stated in that example, it would appear that the same experimental results are reported in Border W.A. et al. (Nature 1990; 346: 371-374). That document discloses the injection of 1ml anti-TGF-β1 antiserum to rats to treat glomerulonephritis (see Figure 2).

The anti-TGF-β1 antiserum was obtained from rabbits. Antibodies are contained in the immunoglobulin fraction of serum. Rabbit serum contains about 8mg immunoglobulin/ml, while the volume of blood in the young rats used in the experiment would be about 11ml. Therefore the circulating concentration of injected immunoglobulin in the rats following the injection of 1ml of the anti-TGF-β1 antiserum would have been about 700 μg/ml. This dose (a 1:11 dilution volume:volume) is comparable to the 1:10 dilution (volume:volume) shown to be effective in blocking TGF-β1-induced inhibition of thymidine incorporation in related studies of this antiserum, whereas a 1:30 dilution (approximately 270 μg immunoglobulin/ml) gave only partial blocking (see figure 1 in Border et al., 1990).

In relation to claims 34 to 38, as discussed above, we respectfully submit that the document cited by the Examiner does not disclose a method for preventing or controlling cataract or after-cataract formation. Further, for the reasons discussed above, the document does not disclose an ophthalmological formulation. Accordingly, we submit the use of claims 34 to 38 is not anticipated by WO 91/04748.

CONCLUSION

Applicant has attempted to respond to each and every rejection set forth in the outstanding Office Action. In view of the above amendments and remarks, Applicant respectfully requests that the application be reconsidered, the claims allowed and the application passed to issue.

Attached hereto is a marked-up version of the changes made to the claims by the current Amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

FULWIDER PATTON LEE & UTECHT, LLP

By: _____

John V. Hanley
Registration No. 38,171

JVH/kst
Howard Hughes Center
6060 Center Drive, Tenth Floor
Los Angeles, CA 90045
Telephone: (310) 824-5555; Facsimile: (310) 824-9696
Customer No. 24201

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

14. (Amended) A method of preventing or controlling cataract or cataract-like disorders in the eye of a mammalian subject which comprises the step of [administrating]administering to the subject an effective amount of one or more inhibitors of TGFβ.

24. (Amended) A method of preventing or controlling [aftercataract]after-cataract formation in the eye of a mammalian subject following lens implant surgery which comprises the step of implanting in the eye of the subject a lens coated with one or more TGFβ inhibitors.

38. (Amended) The method according to claim 35 wherein the proteoglycan inhibitors of TGFβ are selected from decorin, [heparin]heparan sulfate proteoglycans and biglycan.